CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-986

CHEMISTRY REVIEW(S)

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA #: 20-986
CHEMISTRY REVIEW #: 3 DATE REVIEWED: 15-SEP-1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
ORIGINAL	15-SEP-1998	18-SEP-1998
AMENDMENT	20-AUG-1999	23-AUG-1999
AMENDMENT	26-AUG-1999	27-AUG-1999

NAME & ADDRESS OF APPLICANT: Novo Nordisk Pharmaceuticals, Inc.
Suite 200, 100 Overlook Center
Princeton NJ 08450

DRUG PRODUCT NAME

Proprietary:	NovoLog
Established:	insulin aspart (rDNA origin)
Code Name/#:	X-14
Chem.Type/Ther.Class:	1-P

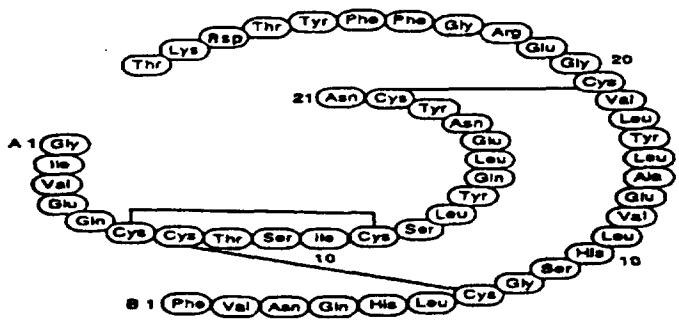
ANDA Suitability Petition / DESI / Patent Status: The applicant holds US patent 5,618,913 which claims Insulin Aspart, and drug product containing Insulin Aspart.

PHARMACOLOGICAL CATEGORY/INDICATION: antihyperglycaemic

DOSAGE FORM:	Solution for Injection
STRENGTHS:	100 U/mL
ROUTE OF ADMINISTRATION:	sc injection
DISPENSED:	X Rx ___ OTC
SPECIAL PRODUCTS:	X Yes ___ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Insulin aspart



SUPPORTING DOCUMENTS:
See review #1

RELATED DOCUMENTS:
IND —

NDA: 20-986

APPEARS THIS WAY
ON ORIGINAL

CONSULTS:

See review #1

REMARKS:

This review includes revised carton labels provided by the applicant in the two amendments dated 20 and 26 August, in response to the items noted in Chemistry Review #2. The applicant made the proposed changes, and the carton and vial and cartridge labels are now acceptable. The CDER Office of Compliance has, however, placed a "Withhold" recommendation for the [redacted] facilities (see attached summary report dated 14-SEP-1999), and has also decided on re-inspection of the facilities after the firm has had time to implement changes based on the 483 items. After re-submission, the reviewing chemist will need to request re-inspection of the facilities.

CONCLUSIONS & RECOMMENDATIONS:

This application remains Approvable, due to the "Withhold" of a recommendation from the CDER Office of Compliance. No other CMC issues remain, however. The re-inspection request will need to be entered into EES upon receipt of the Applicant's re-submission in response to the "Approvable" letter.

cc:
Org. NDA 20-986
HFD-510/Division File
HFD-510/WBerlin/date
HFD-510/CSO
HFD-510/SMoore
HFD-820/J.Gibbs
R/D Init by: SMoore

/S/
William K. Berlin, Review Chemist

filename: [redacted]

/S/
9/16/99

APPEARS THIS WAY
ON ORIGINAL

AUG 1 2 1999

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA #: 20-986
CHEMISTRY REVIEW #: 2 DATE REVIEWED: 12-AUG-1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
ORIGINAL	15-SEP-1998	18-SEP-1998
AMENDMENT	27-MAY-1999	26-MAY-1999
AMENDMENT	28-MAY-1999	29-MAY-1999

NAME & ADDRESS OF APPLICANT: Novo Nordisk Pharmaceuticals, Inc.
Suite 200, 100 Overlook Center
Princeton NJ 08450

DRUG PRODUCT NAME

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Established:	insulin aspart (rDNA origin)
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ROUTE OF ADMINISTRATION:	sc injection
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SPECIAL PRODUCTS:	X Yes ___ No

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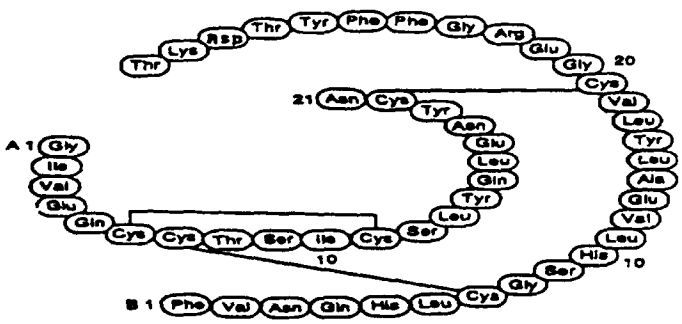
Insulin aspart



SUPPORTING DOCUMENTS:
See review #1

RELATED DOCUMENTS:
IND ——

NDA: 20-986

APPEARS THIS WAY
ON ORIGINAL

CONSULTS:

See review #1

REMARKS:

This review covers labeling and the applicant's response to the deficiencies noted in review #1, contained in the amendment dated 10-AUG-1999. They are acceptable. The Office of Compliance has not yet provided a recommendation for the manufacturing facilities, as of yet, however, and so the application remains "Approvable" based on CMC review.

CONCLUSIONS & RECOMMENDATIONS:

This application is 'Approvable' pending a recommendation from the CDER Office of Compliance for the Novo Nordisk manufacturing facilities and the applicant's inclusion of the minor labeling changes noted herein. There are no Phase IV chemistry commitments required of the applicant.

cc:
Org. NDA 20-986
HFD-510/Division File
HFD-510/WBerlin/date
HFD-510/CSO
HFD-510/SMoore
HFD-820/J.Gibbs
R/D Init by: SMoore

/S/

William K. Berlin, Review Chemist

filename:

/S/
5/12/99

APPEARS THIS WAY
ON ORIGINAL

7/28/99

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA #: 20-986
CHEMISTRY REVIEW #: 1 DATE REVIEWED: 28-JUL-1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE
ORIGINAL	15-SEP-1998	18-SEP-1998
AMENDMENT	21-JAN-1999	22-JAN-1999
AMENDMENT	29-JAN-1999	1-FEB-1999
AMENDMENT	19-FEB-1999	22-FEB-1999
AMENDMENT	15-MAR-1999	16-MAR-1999
AMENDMENT	25-MAY-1999	26-MAY-1999
AMENDMENT	8-JUN-1999	9-JUN-1999
AMENDMENT	10-JUN-1999	11-JUN-1999
AMENDMENT	15-JUN-1999	16-JUN-1999
AMENDMENT	21-JUN-1999	22-JUN-1999
AMENDMENT	13-JUL-1999	14-JUL-1999
AMENDMENT	21-JUL-1999	11-JUL-1999

NAME & ADDRESS OF APPLICANT: Novo Nordisk Pharmaceuticals, Inc.
Suite 200, 100 Overlook Center
Princeton NJ 08450

DRUG PRODUCT NAME

Proprietary:	NovoLog
Established:	insulin aspart (rDNA origin)
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Chem.Type/Ther.Class:	1-P

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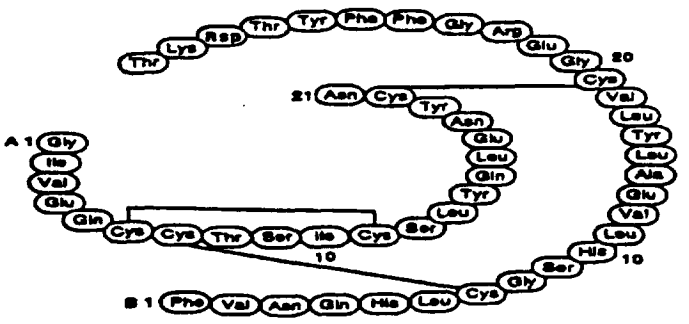
Insulin aspart



SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
—	—	—	Adequate	7-21-99	N/A
—	—	—	Adequate	7-21-99	N/A

—	—	—	Inadequate [1]	1-27-99	2-8-99
—	—	—	Adequate [1]	12-12-98	N/A
—	—	—	N/A (Type I) [1]		

1. Adequate control information

RELATED DOCUMENTS:
IND —

NDA: 20-986

CONSULTS:
Labeling and Nomenclature consult: The applicant requested the name ——— in the original application. This name was found unacceptable to the LNC due to its suggestive nature and potential for confusion. The applicant then submitted the proposed name NovoLog. The LNC found this name to be acceptable (see attached copy of the LNC consult review).

REMARKS:

This application provides information for a recombinant insulin analogue, namely insulin aspart. The primary structure of the molecule is identical to that of human insulin with the exception of a Proline to Aspartic acid mutation at the — position. This results in a ——— of the B-terminus that disrupts hexamer formation and lowers the binding constant. The functional result of this mutation is a more rapid PK (t_{max}) for the drug, compared to regular human insulin, after s.c. administration. The ——— system for this drug is functionally identical to that utilized by this manufacturer for insulin human, and is produced in the same *S. cerevisiae* cells, ——— The product is equipotent to human insulin on a molar basis, as demonstrated in two animal assays, as well as in clinical trials. The product will be distributed in a preserved aqueous formulation at 100 U/ml, as is standard for insulin drug products. Drug product presentations include the usual 10 ml vials, and cartridges of ——— 3.0 ml for use in refillable or disposable insulin pens. The only drug product container/closure component provided for in this application that is not already in use with the applicant's other insulin products, is a ——— stopper to be used with both vials and cartridges. The product-contact surface of the new stopper is identical to that for the original stopper, however. The applicant has adopted the trade name of "NovoLog", and this proposal was found to be acceptable to the labeling and nomenclature committee (see attached consult review). The inspection recommendation for this application is pending, as an extensive 483 was issued during the inspection, and the applicant has yet to reply. The application has been reviewed by the CDER office of Microbiology staff, and it has been recommended for approval on the basis of assurance of sterility. The labeling review for this drug product will be deferred to chemistry review #2.

CONCLUSIONS & RECOMMENDATIONS:

This application is approvable pending the applicant's response to the items contained in the draft letter at the end of this review and pending a final recommendation by the Office of Compliance for the manufacturing facilities. The items in the Draft Letter should be forwarded to the applicant as soon as possible.

cc:
Org. NDA ## ###
HFD-510/Division File
HFD-510/WBerlin/date
HFD-510/CSO
HFD-510/SMoore
HFD-102/JJGibbs [#1 only]
R/D Init by: SMoore

/S/

William K. Berlin, Review Chemist

filename: ———

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/S/
1/28/99

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